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PERKINS COIE LLP			MABRY, JOHN	
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SEATTLE, WA 98111-1208			PAPER NUMBER	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentprocurement@perkinscoie.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/588,883	<b>Applicant(s)</b> AN ET AL.	
	<b>Examiner</b> JOHN MABRY	<b>Art Unit</b> 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 08 November 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                    | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Response to Applicant's Remarks***

Applicant's response on 11/8/10 filed in response to the Office Action dated 5/6/10 has been received and duly noted.

In view of this response, the status of the rejections/objections of record is as follows:

### ***Status of the Claims***

Claims 1-17 are pending and rejected.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

For purposes of convenience, the rejection is repeated below. Examiner remarks to Applicant's arguments will immediately follow.

Rejection of claims 1-17 under 35 U.S.C. 103(a) as being unpatentable over US 5,430,054, in view of US 5,192,817 and in further view of Beroza (JACS 1953, 75, 44-49 and JACS 1952, 74, 1585-1588) are maintained.

The instant application claims a method of purifying an extract of *Tripterydium wilfordii* plant material containing triptolide and related compounds, wherein the extract is formed by

(a) extracting plant materials with aqueous ethanol, and concentrating to obtain a residue; and

(b) forming a slurry of this residue in a chlorinated organic solvent, specifically chloroform, methylene chloride, dichloromethane and mixtures thereof; partitioning the slurry with water and then removing the water;

and said purifying comprises the steps of further partitioning the slurry with an aqueous solution of base, specifically water soluble hydroxide, carbonate or bicarbonate having a counterion selected from lithium, sodium, potassium, cesium ammonium and tetraalkylammonium, and removing a portion of the organic solvent from the slurry; washing the residue with lipophilic solvent, specifically hydrocarbon solvents such as

linear, branched and cyclic hydrocarbons and mixtures thereof; and eluting the residue from silica gel absorbent, specifically silica gel chromatography.

### ***Scope & Content of Prior Art MPEP 2141.01***

US '054 discloses a process of extraction of leaves of *Tripterygium wilfordii* with aqueous ethanol then concentrated to obtain a concentrate (residue). The concentrate (residue) was then distributed in a solution of chloroform-water then the solute in chloroform was concentrated and isolated then eluted through a chromatographic column (see Example 4, bottom of column 9 and top of column 10).

### ***Differences between Prior Art & the Claims MPEP 2141.02***

The disclosure of US '054 differs with the instantly claimed application at the following step:

The extracted residue in the first claimed step is comprised of further partitioning the slurry with an aqueous solution of base, specifically water soluble hydroxide, carbonate or bicarbonate having a counterion selected from lithium, sodium, potassium, cesium ammonium and tetraalkylammonium, and removing a portion of the organic solvent from the slurry; washing the residue with lipophilic solvent, specifically hydrocarbon solvents such as linear, branched and cyclic hydrocarbons and mixtures thereof; then finally elution and isolation of desired extract through column chromatography.

This additional step is implemented to remove significant amounts of impurities at an early stage of the process, thereby increasing yields and reducing production costs. The base treatment removes acidic or weakly acidic compounds such as celastrol, triptoquinone A, triptoquinine G, 3-hydroxyoleanolic acid, popunonic acid, tripterygic acid A, and phenolic compounds such as triptonoterpene, hypolide, triptophenolide and triptonodial from the organic extract of *Tripterygium wilfordii* extract. The base treatment also removes “oily” impurities from the extract via saponification and/or hydrolysis.

In view of US ‘054 and US ‘817, it is well documented that initial organic extracts of plant materials of extracts of *Tripterygium wilfordii* contain many acidic compounds such as 16-hydroxytriptolide, triptoditerpenic acid A, triptoditerpenic acid B, chlorotriptolide and dichlorotriptolide (see (a) column 10, lines 1-15 of US ‘054; (b) column 3, lines 15-16 of US ‘817). Also included in this list of organic extracts is an extensive list of diterpenoids (see Table 1, pages 9-10, compounds 1-33 and structures on pages 11-13 of R. Milanova – Dissertation, January 1995, Simon Fraser University) as detailed by Milanova.

Beroza further describes that isolated alkaloids of *Tripterygium wilfordii* such as wilforine, wilfordine, wilforgine and wilfortrine, which are part of the initial extracts, can be selectively removed by saponified by using aqueous sodium hydroxide (see M. Beroza JACS 1953, 75, 44-49 and JACS 1952, 74, 1585-1588).

The claimed step of extraction can be carried out by multiple extractions of ethanol and plant material followed by pooling of the extracts (see Summary of the Invention and Description of the Invention, columns 1-2 of US '054). The claimed method can be carried out using extracts of roots, stalks or leaves of *Tripterygium wilfordii* (see column 2, lines 5-7).

***Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413***

It would be obvious to an artisan of ordinary skill in the art to incorporate a saponification step in the purification of *Tripterygium wilfordii* plant material in order to remove undesired wilforine, wilfordine, wilforgine and wilfortrine and derivative thereof in view of the references of Beroza. Undesired wilforine, wilfordine, wilforgine and wilfortrine and derivatives thereof are alkaloid esters which are easily removed via saponification (see both references by Berzoa). This process would result in the isolation of desired triptolide and 16-hydroxy triptolide compounds as claimed via column chromatography.

The adjustment of particular conventional working conditions (e.g. determining result effective amounts of the ingredients beneficially taught by the cited references), as well as adjustment of reaction temperature, reaction time and use of solvents, is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan (*In re* Mostovych, Weber, Mitchell and Aulbach,

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144 USPQ 38). Accordingly, these types of modifications would have been well within the purview of the skilled artisan and no more than an effort to optimize results.

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that “[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” KSR, 550 U.S. at \_\_\_, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include:

- (A) Combining prior art elements according to known methods to yield predictable results;
- (B) Simple substitution of one known element for another to obtain predictable results;
- (C) Use of known technique to improve similar devices (methods, or products) in the same way;
- (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
- (E) “Obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;



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- (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
- (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. See MPEP § 2143 for a discussion of the rationales listed above along with examples illustrating how the cited rationales may be used to support a finding of obviousness. See also MPEP § 2144- §2144.09 for additional guidance regarding support for obviousness determinations.

### ***Examiner's Response to Applicant's Arguments***

Applicant alleges that Examiner's rejection is based on hindsight recognition and the disclosure of Beroza rather than Applicant's actual claim. Applicant further argues that claim 1 is directed to a method of purifying an extract of *Tripterygium wilfordii* (Tw) plant material containing triptolide and related compounds, and does not recite "to remove undesired wilforine, wilfordine, wilforgine and wilfortrine and derivatives."

Examiner is well aware of what Applicant is claiming. Examiner did not make this alleged statement as quoted above. Examiner made the following statement which is a direct excerpt from the Non-Final Office Action - see page 5, first full paragraph. This statement was made in favor of purifying an extract of *Tripterygium wilfordii* plant and related compounds as claimed by Applicant.

Beroza further describes that isolated alkaloids of *Tripterygium wilfordii* such as wilforine, wilfordine, wilforgine and wilfortrine, which are part of the initial extracts, can be selectively removed by saponified by using aqueous sodium hydroxide (see M. Beroza JACS 1953, 75, 44-49 and JACS 1952, 74, 1585-1588).

Applicant claims unpredictable results regarding the claim subject matter. Firstly, Applicant has not submitted the "unpredictable results" in the form of an affidavit or declaration. The proper and acceptable way of submitting unpredictable results would be by way of a properly filed affidavit or declaration. Even though Applicant has not properly submitted the unpredictable results in proper form, Examiner will address Applicant's remarks.

Applicant argues that recent KSR case law indicates that the combination of references in an obviousness rejection would yield predictable results with a reasonable expectation of success. Examiner has met the burden of the guidelines as provided by KSR and the MPEP - see Non-Final Office Action.

Examiner has not used hindsight reasoning to reject instant application. Examiner provided evidence in the art that impurities are present in significant amounts at early stages of the extraction process of *Tripterygium wilfordii* plant materials and related compounds - see bottom of page 4 and top of page 5 of Non-Final Office Action:

In view of US '054 and US '817, it is well documented that initial organic extracts of plant materials of extracts of *Tripterygium wilfordii* contain many acidic compounds such as 16-hydroxytriptolide, triptoditerpenic acid A, triptoditerpenic acid B, chlorotriptolide and dichlorotriptolide (see (a) column 10, lines 1-15 of US '054; (b) column 3, lines 15-16 of US '817). Also included in this list of organic extracts is an extensive list of diterpenoids (see Table 1, pages 9-10, compounds 1-33 and structures on pages 11-13 of R. Milanova – Dissertation, January 1995, Simon Fraser University) as detailed by Milanova.

Applicant argues that the claimed invention simplifies known purification procedures to relatively few steps in comparison to conventional methods. Examiner provided motivation for decreasing steps in the claimed process - see Non-Final Office Action, third paragraph on page 4:

This additional step is implemented to remove significant amounts of impurities at an early stage of the process, thereby increasing yields and reducing production costs. The base treatment removes acidic or weakly acidic compounds such as celastrol, triptoquinone A, triptoquinine G, 3-hydroxyoleanolic acid, popunonic acid, tripterygic acid A, and phenolic compounds such as triptonoterpene, hypolide, triptophenolide and triptonodial from the organic extract of *Tripterygium wilfordii* extract. The base treatment also removes “oily” impurities from the extract via saponification and/or hydrolysis.

In order to further address Applicant's arguments, the following statement is made. An artisan of ordinary skill would be motivated to reduce individual extraction

steps for purposes of convenience, cost, higher yields, etc. This is a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan. A skill artisan would be motivated to take a multi-step process and make it into a process with fewer steps in order arrive at desire product faster and more efficiently.

The adjustment of particular conventional working conditions (e.g. determining result effective amounts of the ingredients beneficially taught by the cited references), as well as adjustment of reaction temperature, reaction time and use of solvents, rearranging steps in a reaction sequence, is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan (*In re Mostovych*, Weber, Mitchell and Aulbach, 144 USPQ 38). Accordingly, these types of modifications would have been well within the purview of the skilled artisan and no more than an effort to optimize results.

As stated above, it is well within the purview of the skilled artisan in the relevant art to reduce steps in order to achieve the desired product faster and in higher yields.

Using theoretical and scientific reasoning, the following statement by Dorwald supports Examiner's statement of motivation. Dorwald clearly states that in the design of a molecule, a synthetic chemist would need to analyze *"the shortest synthetic strategies which are most likely to give rapid access to the target compound, ideally in high yield and purity"* - see page 2 under 1.2 Synthesis Design.

Again, an artisan of ordinary skill, would be motivated to take the prior art of record and reduce the steps in order to achieve the final product for improved efficiency.

Applicant argues that the prior art teaches away from the use of bases by citing the references of March and Chen et al. Although the literature in the art may teach away from the use of a base, Examiner provided motivation for the use of a base in accordance with the claimed invention - see Non-Final Office Action, third paragraph on page 4 (see excerpt above) and first full paragraph on page 5 (see excerpt below):

Beroza further describes that isolated alkaloids of *Tripterygium wilfordii* such as wilforine, wilfordine, wilforine and wilfortrine, which are part of the initial extracts, can be selectively removed by saponified by using aqueous sodium hydroxide (see M. Beroza JACS 1953, 75, 44-49 and JACS 1952, 74, 1585-1588).

For these reasons, the instantly claimed invention are deemed to obvious over the disclosures and teaching of the prior art.

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that “[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” KSR, 550 U.S. at \_\_\_, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include:

(A) Combining prior art elements according to known methods to yield

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- predictable results;
- (B) Simple substitution of one known element for another to obtain predictable results;
  - (C) Use of known technique to improve similar devices (methods, or products) in the same way;
  - (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
  - (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
  - (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
  - (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. See MPEP § 2143 for a discussion of the rationales listed above along with examples illustrating how the cited rationales may be used to support a finding of obviousness. See also MPEP § 2144- §2144.09 for additional guidance regarding support for obviousness determinations.

The aforementioned reasons above describe rationales that support a conclusion of obviousness based upon the KSR International Co. v. Teleflex Inc. decision. Letters (A) and (C) - (E) rationale is supported above.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

### ***Conclusion***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/John Mabry/  
Examiner  
Art Unit 1625

/Janet L. Andres/  
Supervisory Patent Examiner, Art Unit 1625